Human Reference Atlas Construction and Usage: The Breast

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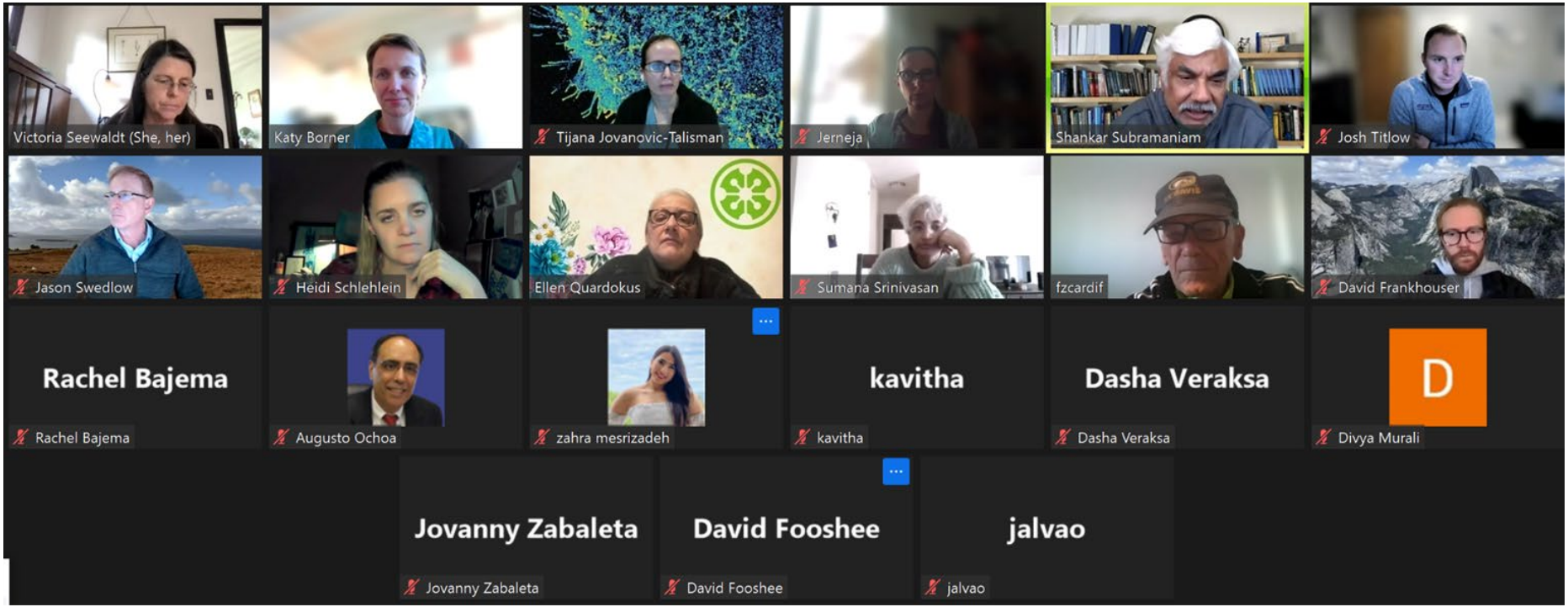
Presentation at LEAP - TNBC Breast Cancer Project, UCSD

November 30, 2022


Victoria Seewaldt (She, her)
Katy Borner
Tijana Jovanovic-Talisman
Jerneja
Shankar Subramaniam
Josh Titlow
Jason Swedlow
Heidi Schlehlein
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Dasha Veraksa
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Outline

HuBMAP & The Human Reference Atlas
- Overview of project
- Human Reference Atlas effort

ASCT+B Tables
- Examples
- How to get involved

FTU Illustrations
- Examples
- How to contribute

3D Model
- Example/RUI
- How to contribute

Questions/Discussion

About HuBMAP

Vision

Catalyze the development of an open, global framework for comprehensively mapping the human body at cellular resolution.

HuBMAP
The Human BioMolecular Atlas Program

https://commonfund.nih.gov/HuBMAP

Accelerate Tools and Technique Development

Accelerating the development of the next generation of tools and techniques for constructing high resolution spatial tissue maps that quantify multiple types of biomolecules either sequentially or simultaneously

Generate 3D Human Tissue Maps

Generating foundational 3D human tissue maps using validated high-content, high-throughput imaging and omics assays

Establish Open Data Platform

Establishing an open data platform that will develop novel approaches to integrating, visualizing and modelling imaging and omics data to build multi-dimensional tissue maps, and making data rapidly findable, accessible, interoperable, and reusable by the global research community

Collaborate with the Research Community

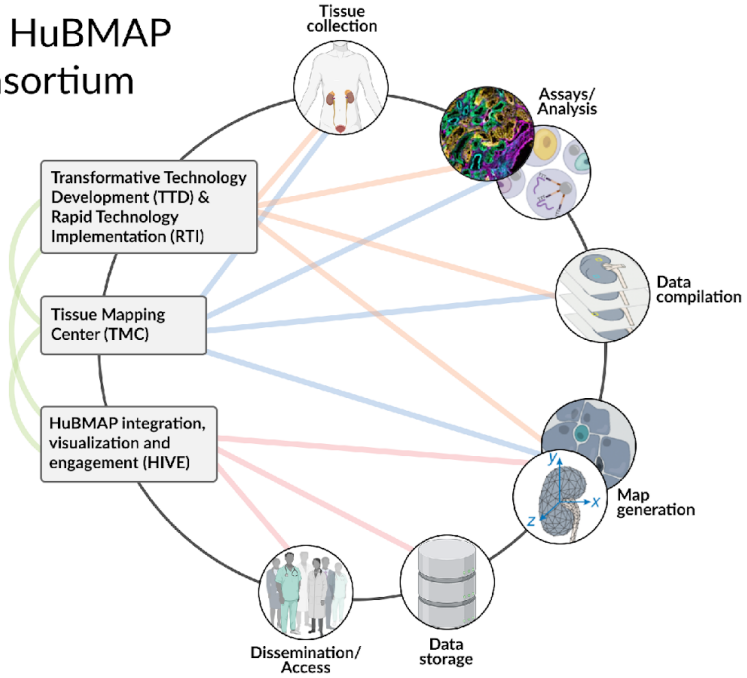
Coordinating and collaborating with other funding agencies, programs, and the biomedical research community to build the framework and tools for mapping the human body at single cell resolution

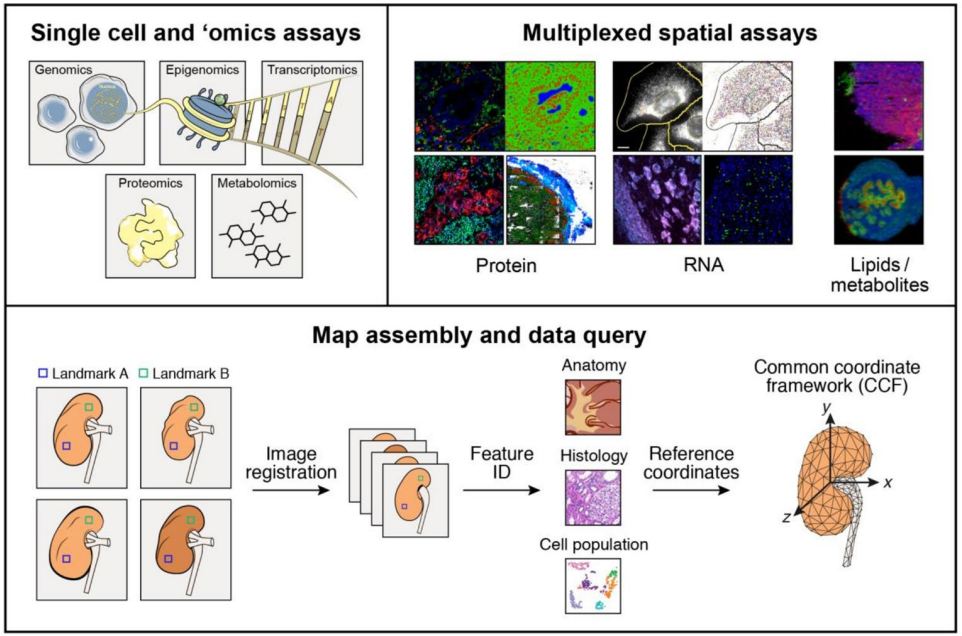
Support Pilot Projects

Supporting pilot projects that demonstrate the value of the resources developed by the program to study normal individual variations and tissue changes across the lifespan and the health-disease continuum

The Human Body at Cellular Resolution: The NIH Human Biomolecular Atlas Program
Snyder et al. *Nature*. 574, p. 187-192.

The HuBMAP Consortium





HuBMAP Funded Groups 2022

Rapid Technology Implementation

Transformative Technolgy Development

Tissue Mapping Centers

HuBMAP Integration Visualization Engagement

27 RTI Members
4 funded groups

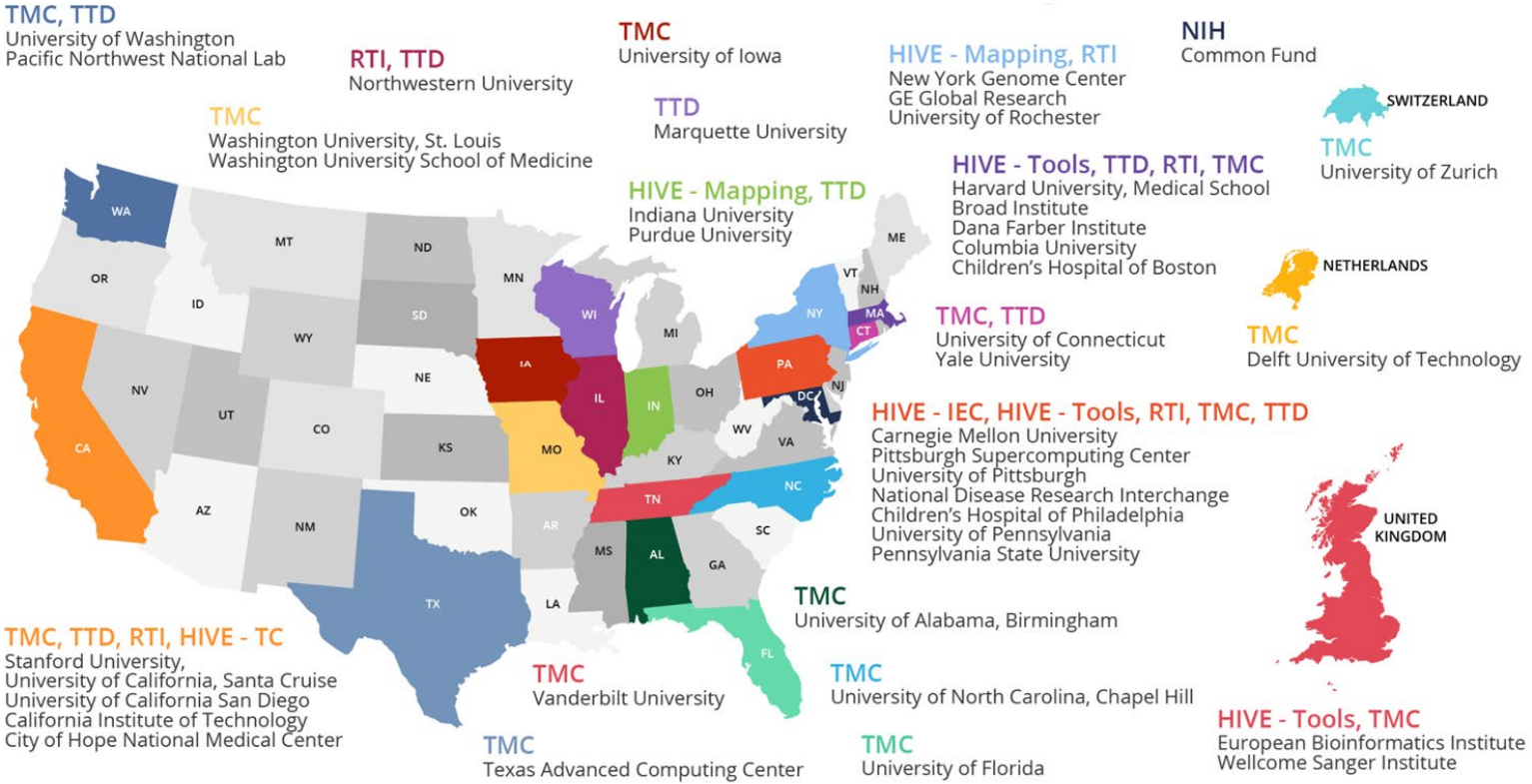
60 TTD Members
8 funded groups

160 TMC Members
11 funded groups

111 HIVE Members
5 funded groups

358 Members in
28 funded groups

HuBMAP Contributing Sites



Setup and Scale Up Phase (2018-2022)

Tool Development
- Standardized Analytical Workflows, Metadata, Protocols
- Multimodal/Multi-scale data generation

3D Maps and Reference Datasets
- HRA Common Coordinate Framework
- ASCT+B & 3D Reference Object Library
- Azimuth

Open Data Platform
- HuBMAP Portal

Outreach and Collaboration
- Summer Internship Program, Jumpstart Program, Kaggle Competition

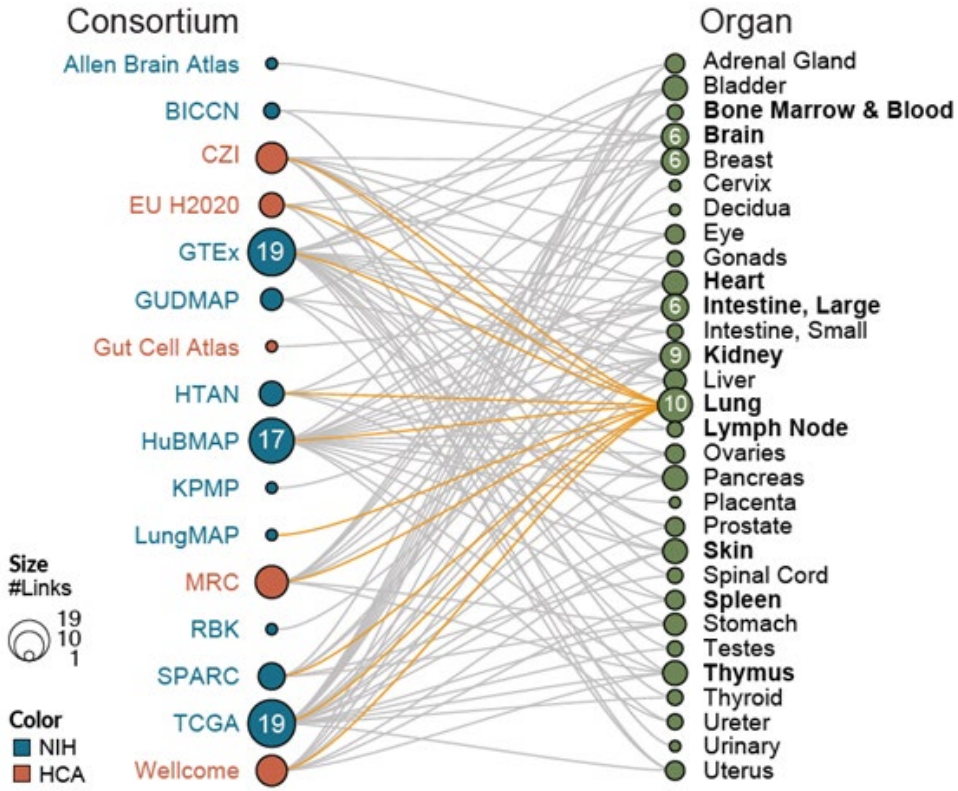
Production Phase (2022 - 2026)

3D Maps and Reference Datasets

- Common data types: RNAseq, multiplexed IF, histology datasets
- Build bridging datasets to link data types, e.g., cell x gene data
- Azimuth maps for: kidney, lung, colon, bone marrow, female reproductive system, pancreas, heart, eye, skin, bone, and lymphatics
- Human Reference Atlas for 30 organs (ASCT+B Tables and associated 3D reference objects)
- Identify and generate 2D reference objects of FTUs at single cell level
- Build out Antibody Characterization / Validation Reports (AVRs) & Organ Mapping Antibody Panels (OMAPs)
- Crosswalk experimental data to the Human Reference Atlas

About
Human Reference Atlas

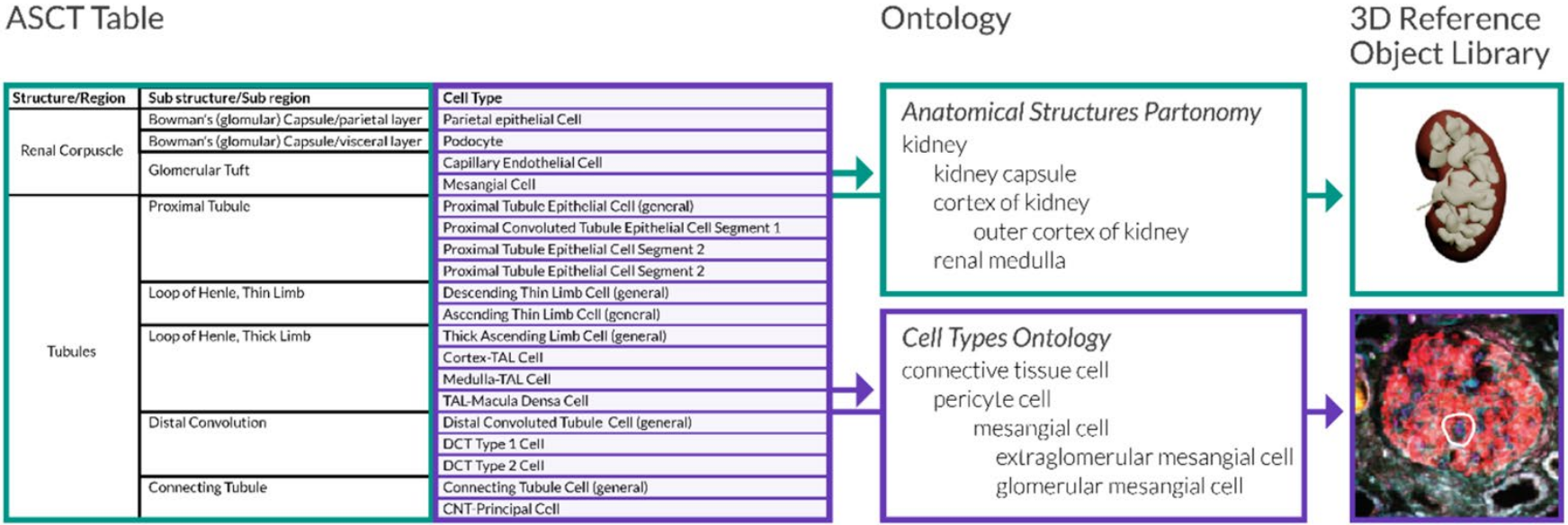
Human Reference Atlas (HRA)



Börner, Katy, Sarah A Teichmann, Ellen M Quardokus, James Gee, Kristen Browne, David Osumi-Sutherland, Bruce W Herr II, Andreas Bueckle, Hrishikesh Paul, Muzlifah A Haniffa, Laura Jardine, Amy Bernard, Song-Lin Ding, Jeremy A Miller, Shin Lin, Marc Halushka, Avinash Boppana, Teri A Longacre, John Hickey, Yiing Lin, M Todd Valerius, Yongqun He, Gloria Pryhuber, Xin Sun, Marda Jorgensen, Andrea J Radtke, Clive Wasserfall, Fiona Ginty, Jonhan Ho, Joel Sunshine, Rebecca T Beuschel, Maigan Brusko, Sujin Lee, Rajeev Malhotra, Sanjay Jain, and Griffin Weber. 2021. "Anatomical structures, cell types and biomarkers of the Human Reference Atlas." *Nature Cell Biology* 23: 1117-1128. doi: 10.1038/s41556-021-00788-6.

Human Reference Atlas (HRA)

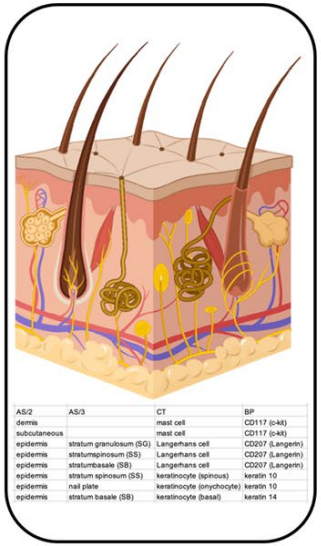
Anatomical Structures, Cell Types, and Biomarkers or ASCT+B tables aim to capture the partonomy of anatomical structures, cell types, and major biomarkers (e.g., gene, protein, lipid or metabolic markers). 3D and 2D reference object capture the shape, size, and spatial composition of ASCT.



Human Reference Atlas (HRA)

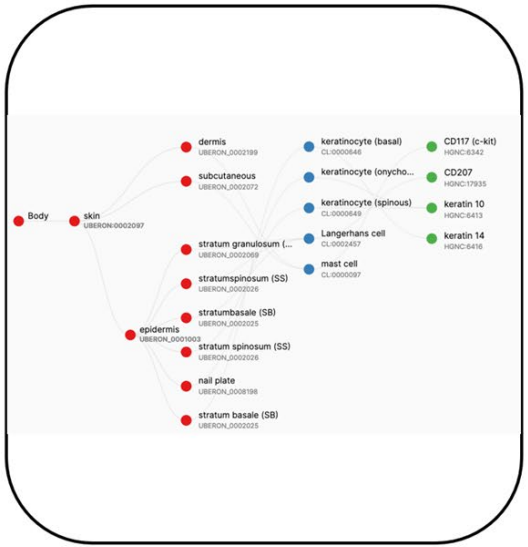
Organ Mapping Antibody Panels (OMAPs) are collections of antibodies that allow spatial mapping of the anatomical structures and cell types present in diverse organs using multiplexed antibody-based imaging.

Skin



AS/2	AS/3	CT	BP
dermis		mast cell	CD117 (c-kit)
subcutaneous		mast cell	CD117 (c-kit)
epidermis	stratum granulosum (SG)	Langerhans cell	CD207 (Langerin)
epidermis	stratumspinosum (SS)	Langerhans cell	CD207 (Langerin)
epidermis	stratumbasale (SB)	Langerhans cell	CD207 (Langerin)
epidermis	stratum spinosum (SS)	keratinocyte (spinous)	keratin 10
epidermis	nail plate	keratinocyte (onychocyte)	keratin 10
epidermis	stratum basale (SB)	keratinocyte (basal)	keratin 14

ASCT + B



4 Affinity Reagent / pBiomarker Pairs

https://hubmapconsortium.github.io/ccf/pages/omap.html

Azimuth References

https://azimuth.hubmapconsortium.org

Azimuth is a web application that uses an annotated reference dataset to **automate the processing, analysis, and interpretation of a new single-cell RNA-seq experiment**. Azimuth leverages a **'reference-based mapping'** pipeline that inputs a counts matrix of gene expression in single cells, and performs normalization, visualization, cell annotation, and differential expression (biomarker discovery). All results can be explored within the app, and easily downloaded for additional downstream analysis.

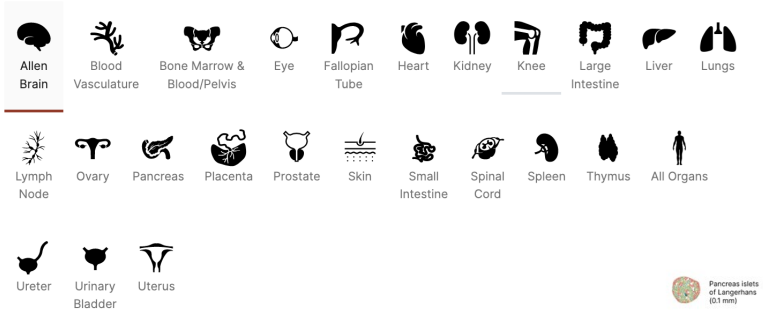
The development of Azimuth is led by the New York Genome Center Mapping Component as part of the NIH Human Biomolecular Atlas Project (HuBMAP).

Human Reference Atlas (HRA) v1.3

ASCT+B Tables: 26 tables

Organ	#AS	#CT	#B Total	#BG	#BP	#AS-AS	#AS-CT	#CT-B
Blood	1	30	159	112	47	1	30	506
Blood Vasculature	918	10	10	10	0	952	2030	11
Bone Marrow	1	47	262	198	64	1	47	838
Brain	183	127	257	257	0	183	127	346
Eye	26	53	140	61	75	27	58	404
Fallopian Tube	72	18	26	13	13	84	81	27
Heart	50	23	45	45	0	60	183	74
Kidney	57	67	184	184	0	72	75	300
Knee	33	41	12	0	12	33	21	47
Large Intestine	54	57	166	83	83	287	1156	360
Liver	17	31	85	29	56	17	32	116
Lung	76	76	280	191	89	121	168	456
Lymph Node	34	45	223	106	117	43	86	499
Lymph Vasculature	31	1	1	1	0	31	19	1
Ovary	77	16	12	0	12	126	30	11
Pancreas	32	34	51	49	2	153	228	126
Peripheral Nervous System	782	1	2	1	1	803	609	2
Placenta	25	22	44	43	0	32	44	74
Prostate	4	12	31	31	0	4	12	36
Skin	15	36	70	0	70	17	19	100
Small Intestine	39	48	89	43	46	69	178	131
Spleen	37	60	194	85	109	50	129	421
Thymus	17	51	394	318	76	28	39	603
Ureter	7	14	30	30	0	7	14	61
Urinary Bladder	16	15	30	30	0	16	16	63
Uterus	61	18	45	39	6	89	34	65
Totals:	**2,665**	**953**	**2,842**	**1,959**	**878**	**3,306**	**5,465**	**5,678**

3D Reference Object Library: 57 organ models, landmark organs, 2 united files, adding L/R breast (mammary gland)



All available via HRA Portal
https://hubmapconsortium.github.io/ccf

HRA User Interfaces/Training

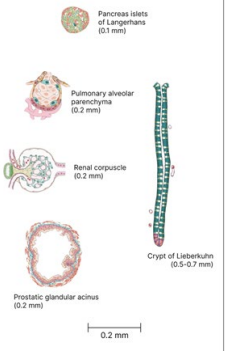
- ASCT+B Reporter
- Registration User Interface (RUI)
- Exploration User Interface (EUI)
- Visible Human MOOC (VHMOOC)

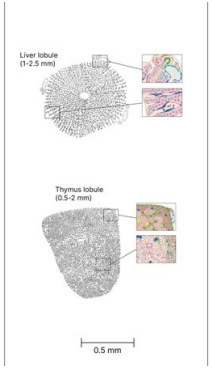
2D FTUs: 19 FTUs

OMAPs: 8 organs

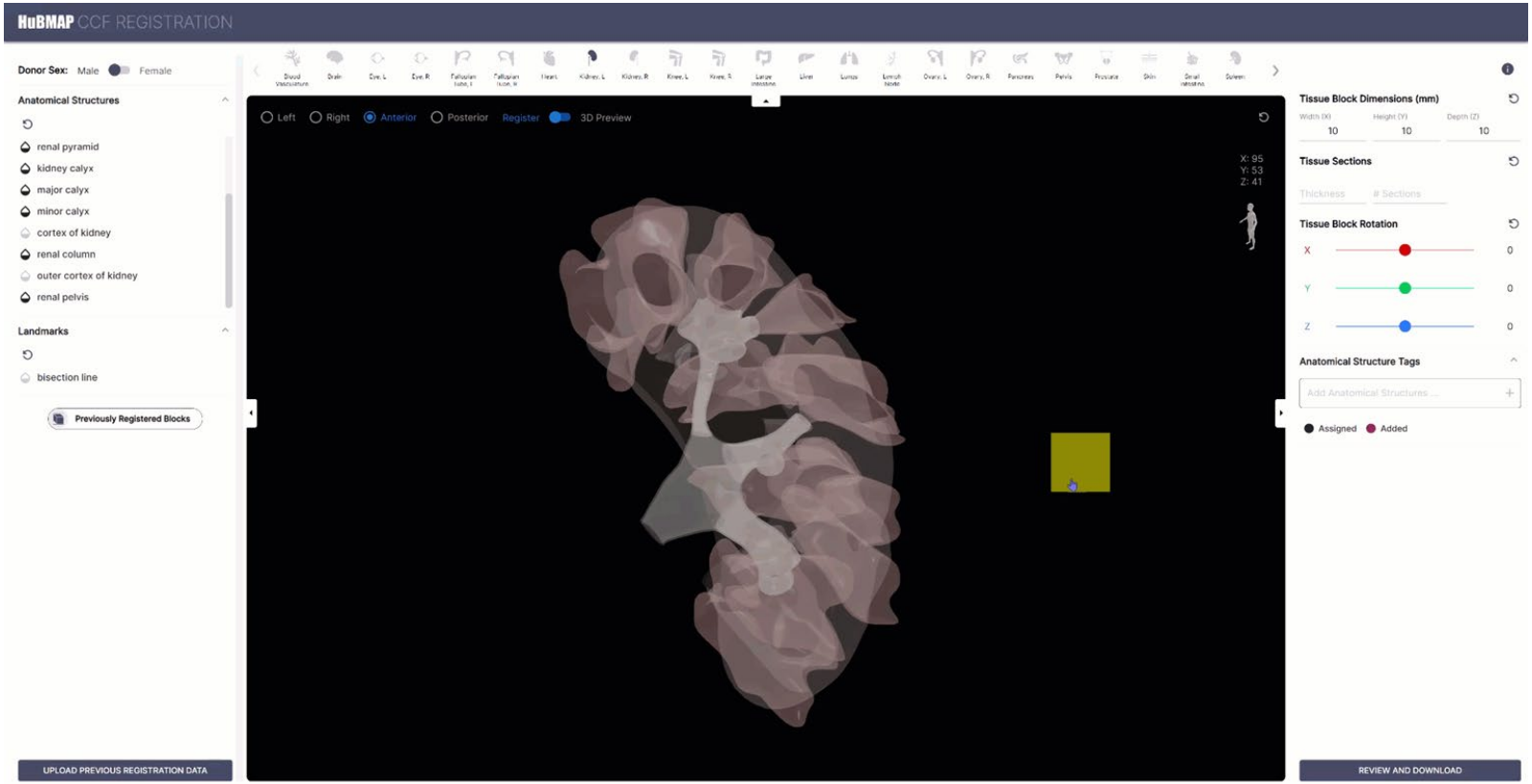
References to **papers**

21 References to **data**
via Kidney Azimuth from Blue Lake et al. paper with 21 tissue blocks



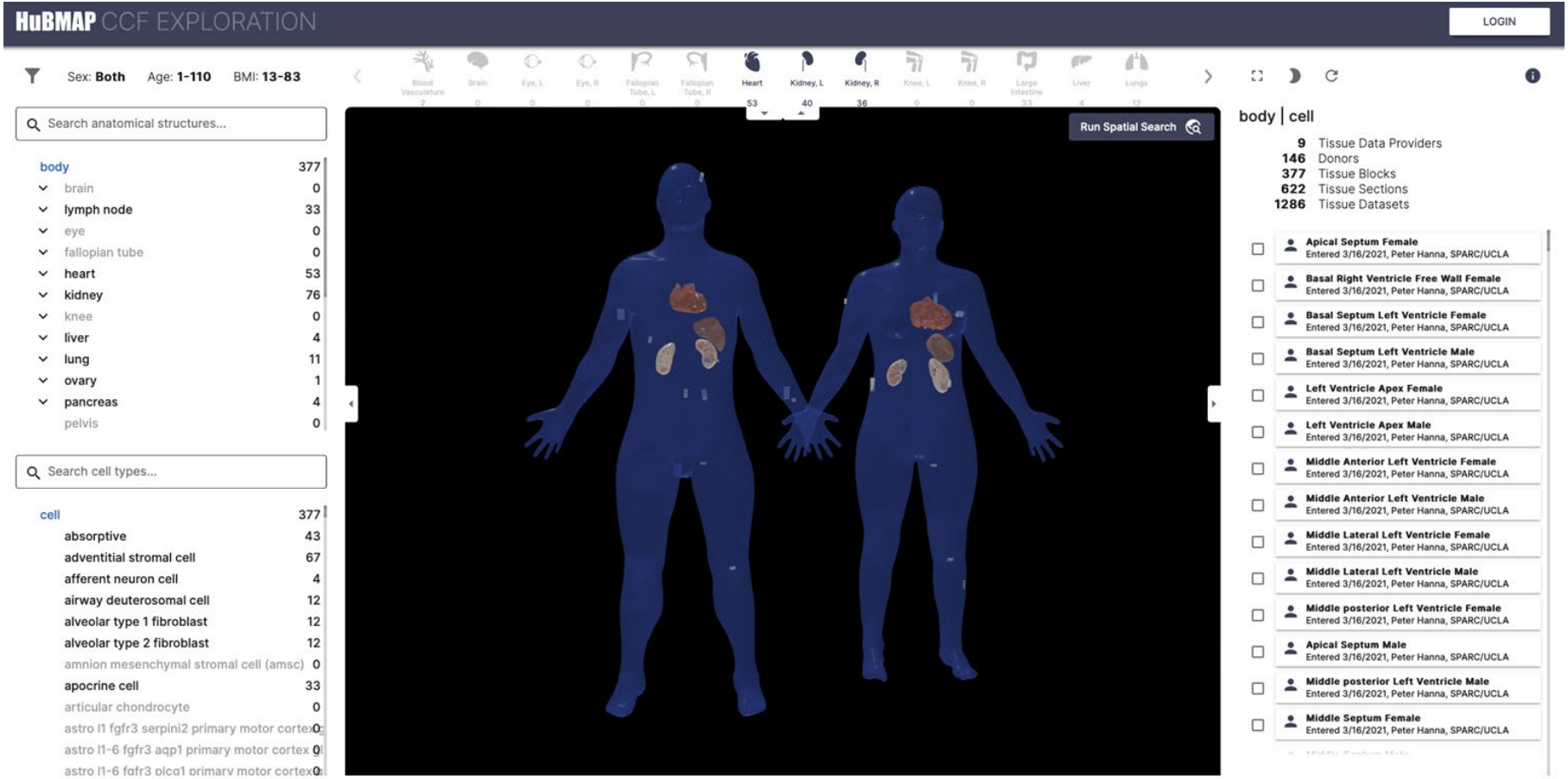


Registration User Interface (RUI)



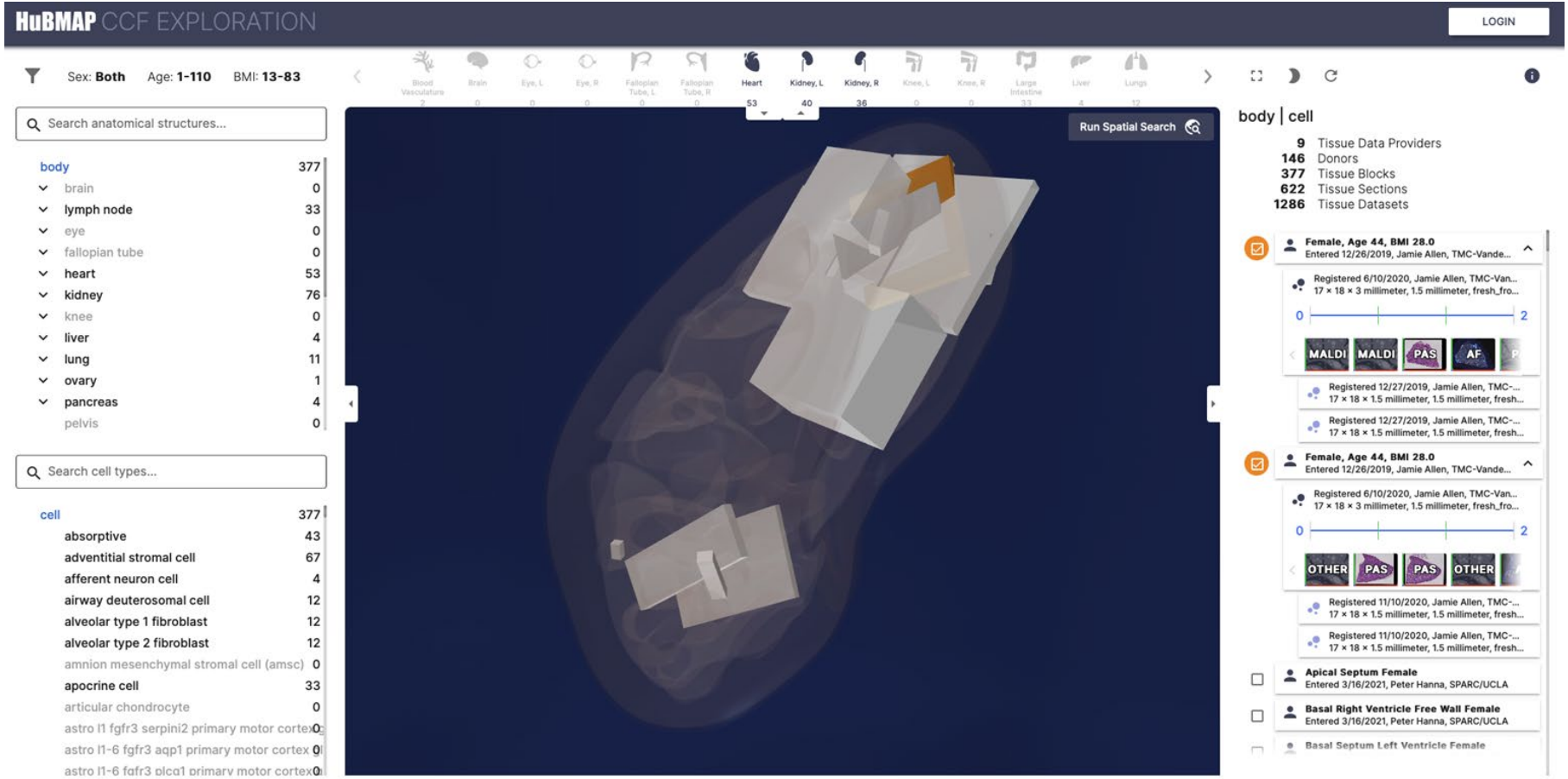
https://hubmapconsortium.github.io/ccf-ui/rui/

Exploration User Interface (EUI)



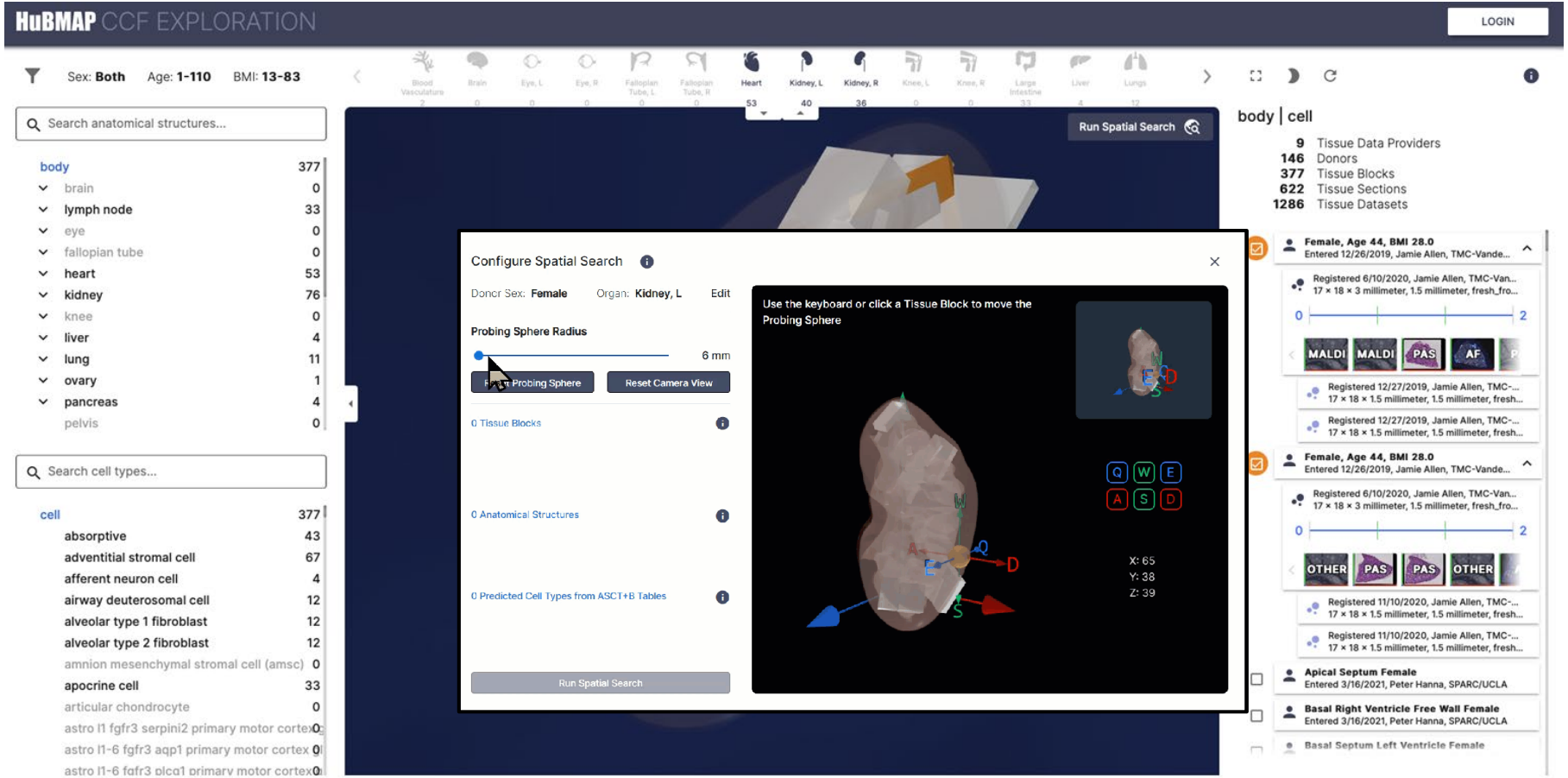
https://portal.hubmapconsortium.org/ccf-eui

Exploration User Interface (EUI)



https://portal.hubmapconsortium.org/ccf-eui

Exploration User Interface (EUI) - Spatial Search



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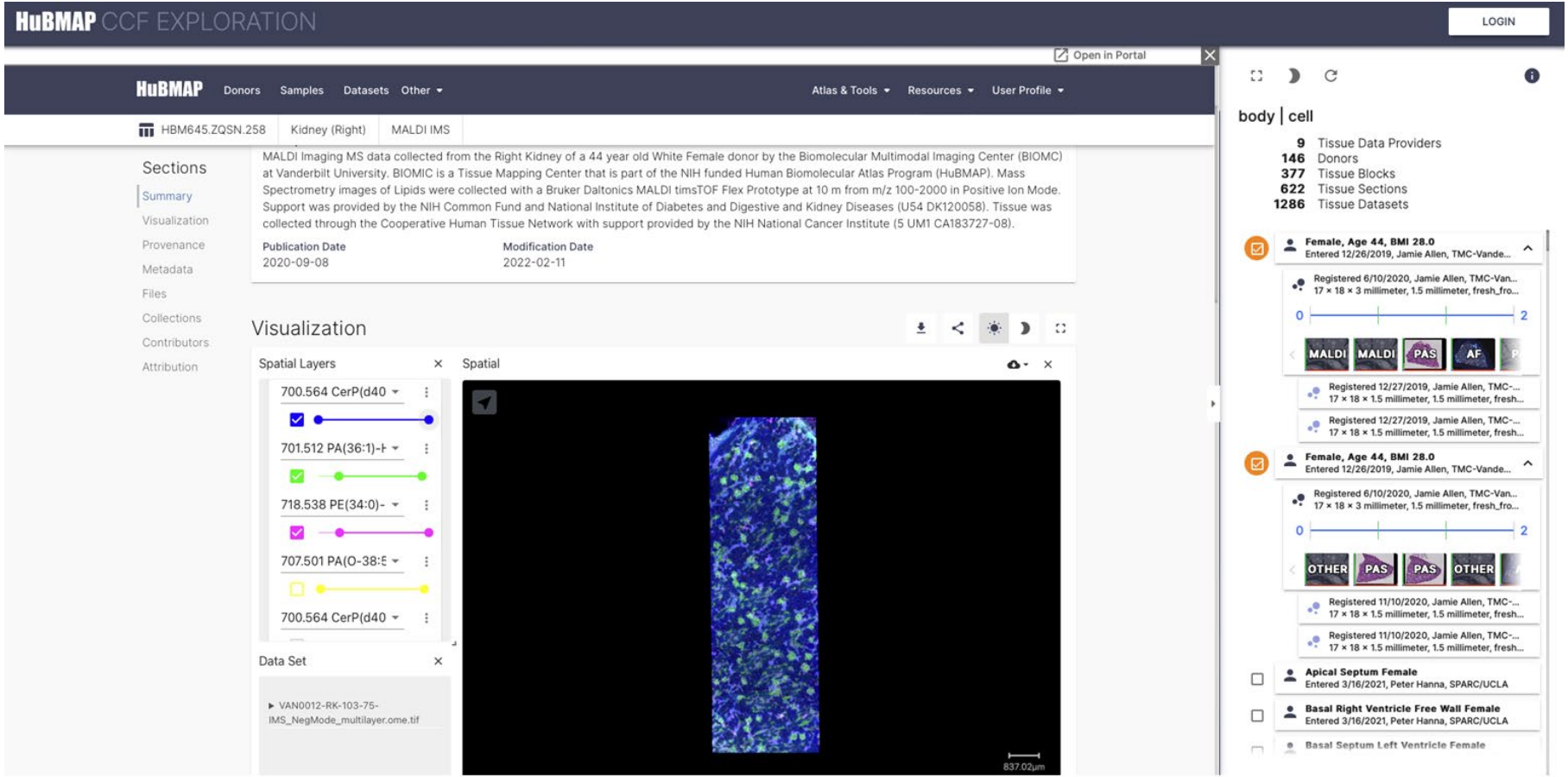
Exploration User Interface (EUI) & Vitessce



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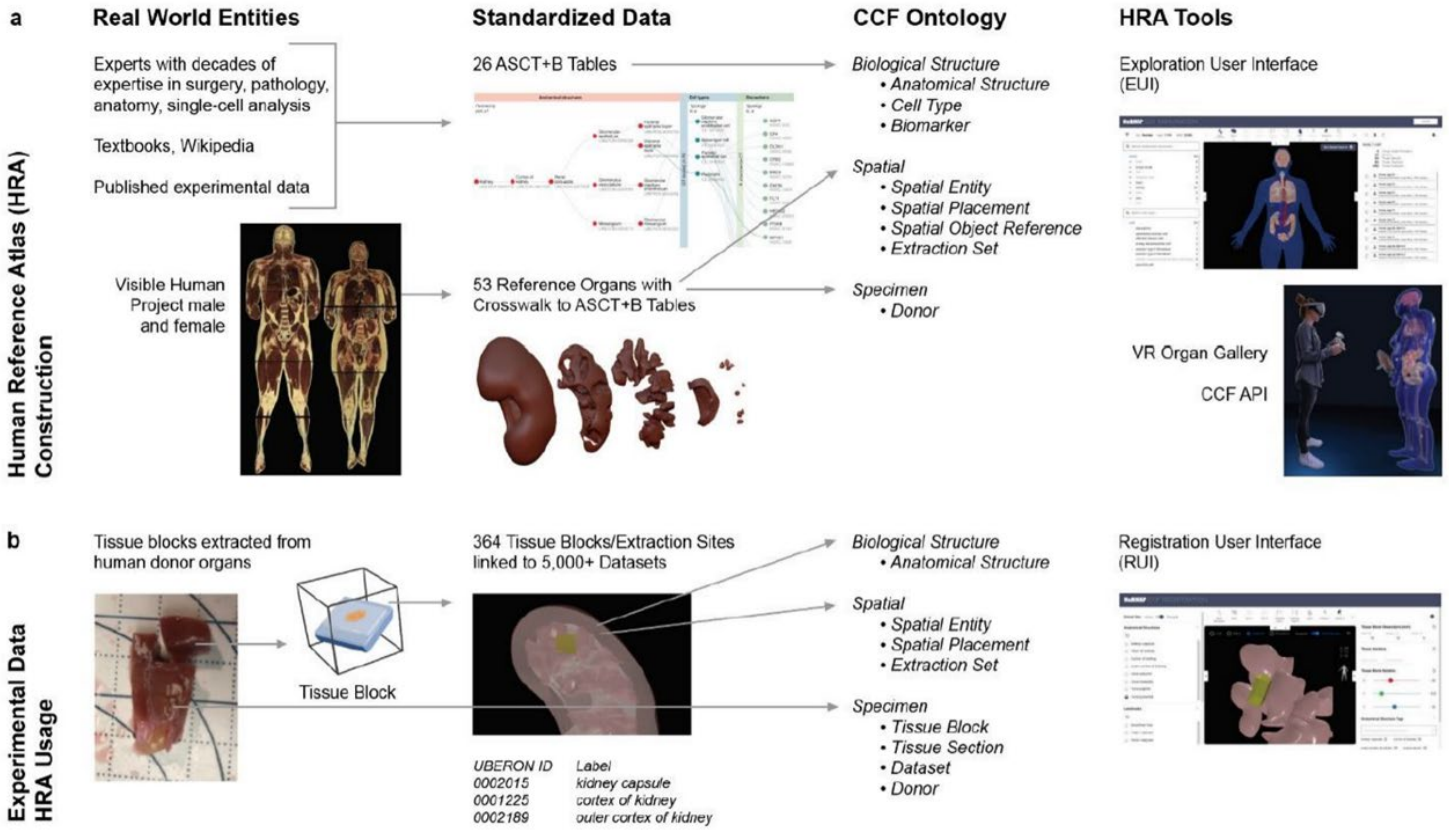


Figure 1. From real-world entities, to standardized data, to ontology. a. Human Reference Atlas construction takes real-world data and represents it in standardized data structures that are defined by the interlinked Biological Structure, Spatial, and Specimen ontologies.

Specimen, Biological Structure, and Spatial Ontologies in Support of a Human Reference Atlas

https://biorxiv.org/cgi/content/short/2022.09.08.507220v1

ASCT+B Tables

Breast ASCT+B Table

Goals and objectives

Capture relationships between Anatomical structures (AS), cell types (CT) and biomarker (B) sets that uniquely define those cell types for Breast

- Anatomical structures: gross, macro and microscopic levels
- Cell types present in each of the anatomical structures
- Biomarker sets that uniquely define a cell type for cell type annotation
- Proteins (proteoforms, transcription factors etc), single cell transcriptomics differentially expressed genes, metabolites, lipids, spatial transcriptomics, multi-omic (CITE-seq)
- Map all AS, CT, Biomarker types to standard ontologies (uberon, cell ontology, HGNC, UniProt, LipidMaps, METLIN and Human Metabolome Databases)
- Working with Harikrishna Nakshatri from Indiana University School of Medicine and Susan G. Komen Tissue Bank at IU Simon Comprehensive Cancer Center for spatial transcriptomics and transcriptomics

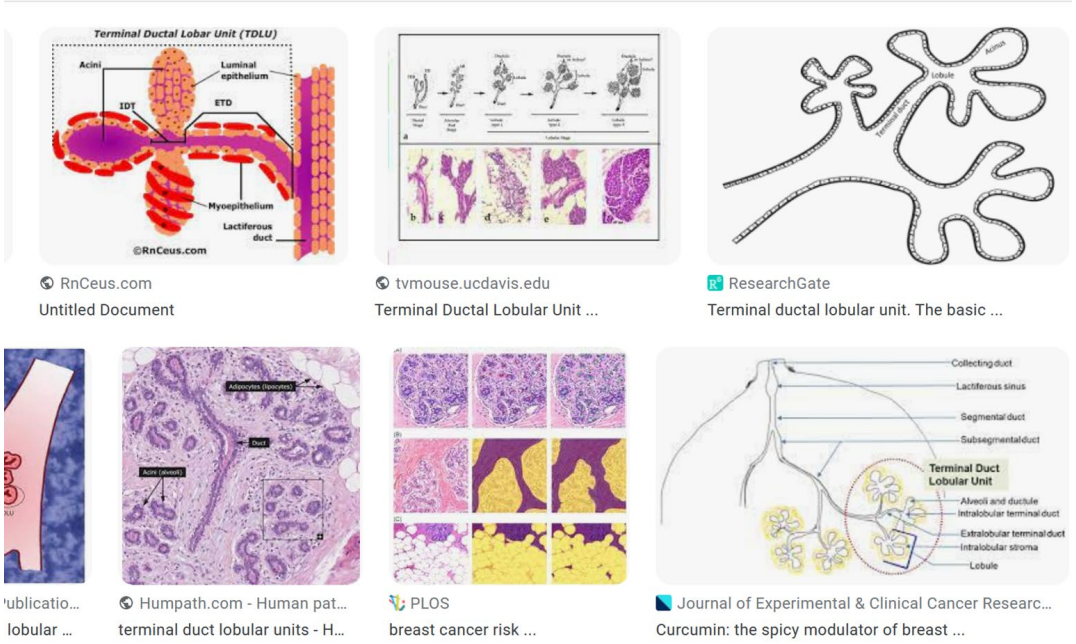
FTU Illustrations

Breast 2D Functional Tissue Units (FTUs)

Illustrate functional tissue unit(s) for breast. Currently published as static images on the CCF portal. Next cycle published with interactive functionality, linked to data.

Potential FTUs for Breast:

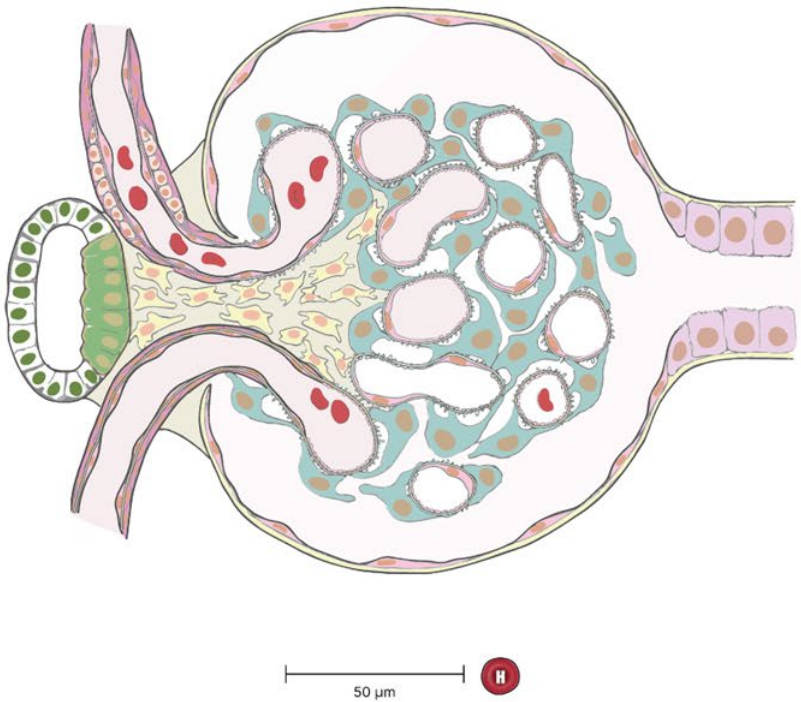
- *Terminal duct lobular unit (TDLU)*
- Acius
- Lactiferous sinus
- Segmental duct



FTU Library

- Kidney
  - Ascending thin limb
  - Cortical collecting duct
  - Collecting duct (inner medulla)
  - Collecting duct (outer medulla)
  - Descending thin limb
  - Nephron
  - Renal corpuscle
- Large intestine
  - Crypt of Lieberkuhn
- Liver
  - Liver lobule
- Lung
  - Pulmonary alveolar parenchyma
  - Bronchial submucosal gland
- Pancreas
  - Acinus
  - Intercalated duct
  - Islets of Langerhans
- Prostate
  - Prostatic glandular acinus
- Skin
  - Dermal papilla
  - Epidermal ridge
- Spleen
  - Red pulp
  - White pulp
- Thymus
  - Thymus lobule

Renal Corpuscle of the Kidney



Cell Types by Gene Biomarkers

Expand

Gene Biomarkers | Protein Biomarkers | Lipid Biomarkers

Cell Type	Cell Count	VCAM1	CLDN1
parietal epithelial cell	5,758	●	●
glomerular visceral epithelial cell	13,224		
glomerular capillary endothelial cell	2,028		
glomerular mesangial cell	no data		

Gene Expression Mean in FTU: 0.0 – 1.0

Percentage of cells in FTU: 0% – 100%

Source Data

1. Kidney Precision Medicine Project
   Ancillary Study Data, Clinical Data, HRT Codebook
2. [Dataset Owner Title]
   <Dataset Title + Link to Dataset>
3. [Dataset Owner Title]
   <Dataset Title + Link to Dataset>
4. [Dataset Owner Title but extremely long and wraps around to the next line as you can see here in this example]
   <Extremely long dataset title that wraps around to the next line as you can see in this example + link to dataset>
5. [Dataset Owner Title]
   <Dataset Title + Link to Dataset>
6. [Dataset Owner Title]

Illustration | Embed | Contact | HRA Portal

3D model of breast

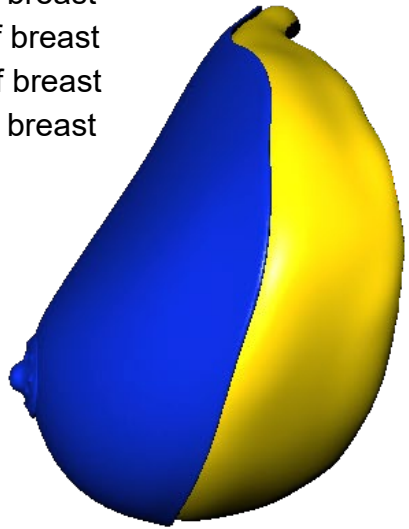
Human female mammary gland model

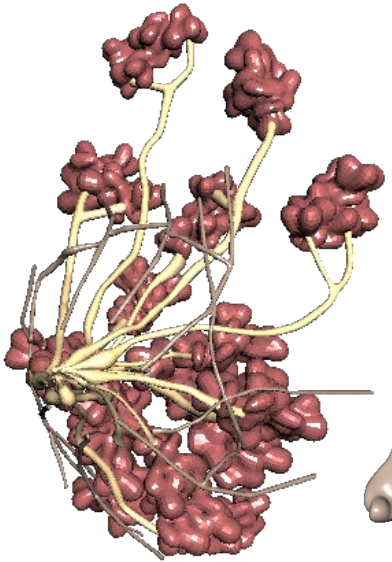
Created for use in Registration User Interface (RUI)

List of Anatomic Structures

Mammary gland (F):

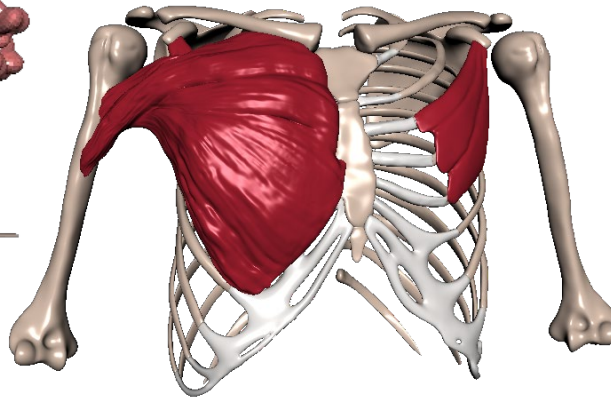
- lower inner quadrant of breast
- lower outer quadrant of breast
- upper inner quadrant of breast
- upper outer quadrant of breast
- suspensory ligament of breast
- axillary tail of breast
- mammary lobes
- areolar tubercle
- main lactiferous duct
- lactiferous sinus
- fad pads
- nipples
- areolas

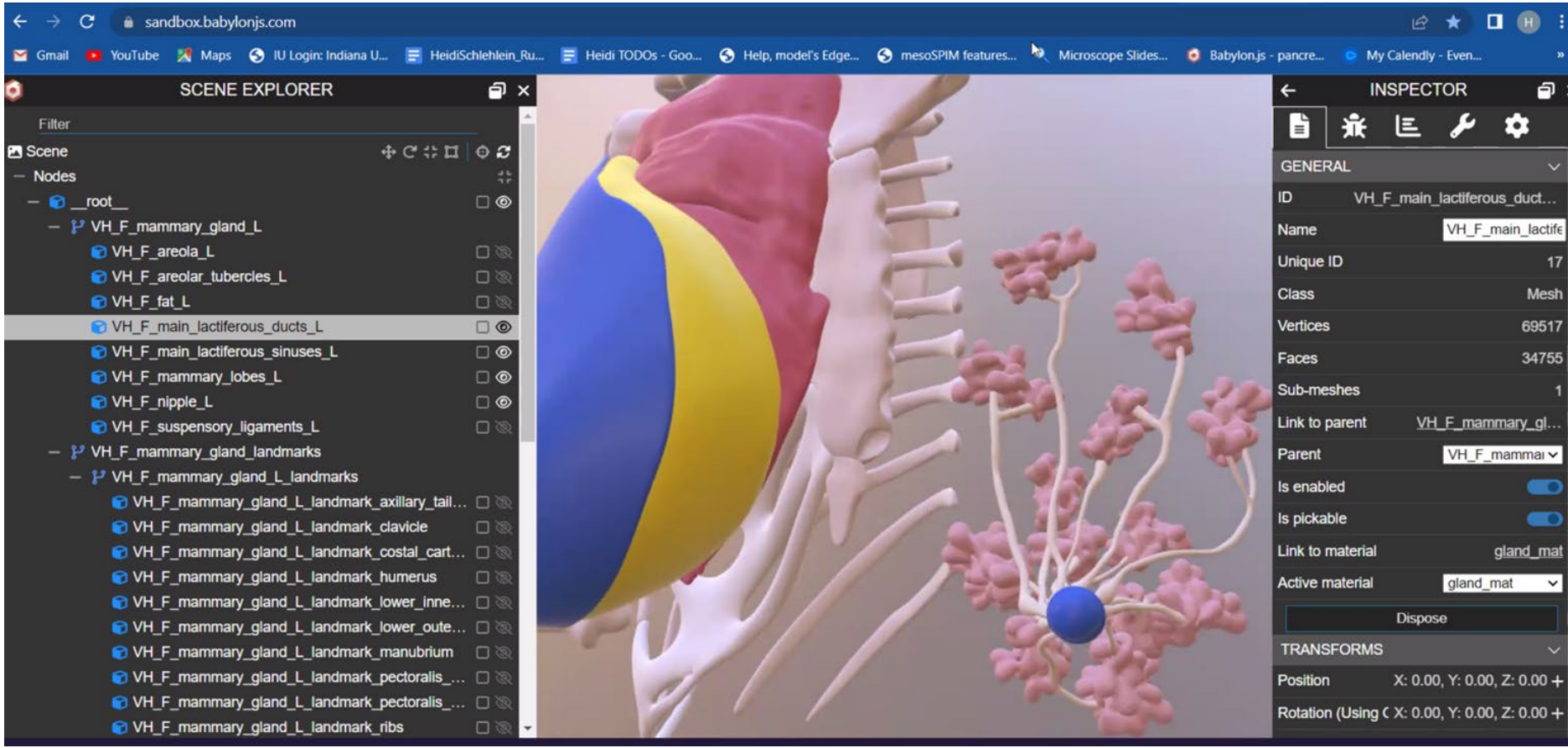




Landmarks (F):

- manubrium, sternum, xiphoid process
- pectoralis major (2)
- Pectoralis minor (2)
- Clavicles (2)
- Humerus (2)
- Ribs (2x12)
- Costal cartilage (2x6)




sandbox.babylonjs.com
Gmail
YouTube
Maps
IU Login: Indiana U...
HeidiSchlehlein_Ru...
Heidi TODOs - Goo...
Help, model's Edge...
mesoSPIM features...
Microscope Slides...
Babylon.js - pancre...
My Calendly - Even...
SCENE EXPLORER
Filter
Scene
Nodes
__root__
VH_F_mammary_gland_L
VH_F_areola_L
VH_F_areolar_tubercles_L
VH_F_fat_L
VH_F_main_lactiferous_ducts_L
VH_F_main_lactiferous_sinuses_L
VH_F_mammary_lobes_L
VH_F_nipple_L
VH_F_suspensory_ligaments_L
VH_F_mammary_gland_landmarks
VH_F_mammary_gland_L_landmarks
VH_F_mammary_gland_L_landmark_axillary_tail...
VH_F_mammary_gland_L_landmark_clavicle
VH_F_mammary_gland_L_landmark_costal_cart...
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VH_F_mammary_gland_L_landmark_lower_inne...
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Faces 34755
Sub-meshes 1
Link to parent VH_F_mammary_gl...
Parent VH_F_mammai
Is enabled
Is pickable
Link to material gland_mat
Active material gland_mat
Dispose
TRANSFORMS
Position X: 0.00, Y: 0.00, Z: 0.00
Rotation (Using C X: 0.00, Y: 0.00, Z: 0.00

Questions / Discussion